Helicobacter pylori

&

Gastric MALT Lymphoma

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Helicobacter pylori and Gastric MALT Lymphoma

Background

- Most extra nodal lymphomas arise in Stomach
  - G'M'L
- Isaacson 1983: Marginal zone B L ; Indolent localized at diagnosis
- *H pylori*: the leading cause (Development, progression); 60-90% regression after *Hp* eradication *(Fischbach, 2004)*
Increasing GL incidence in Algerians

- 67 % of GI lymphomas
- 37 % of gastric cancers Vs 10 % *

Average mean age at 44 years in Algerian population /
→ 2 decades younger than in occident (61 y)*
→ 25% < 30 years old (serum immunoelectrophoresis
careful endoscopy + duodeno-jejunal biopsies to
exclude the extension to the stomach of an IPSID)

No difference according to gender (M/F ratio : 1/1.2)*

* OMS, 2008
*Anon, Blood 1997
G'M'L: PRECURSOR LESIONS

→ *H. pylori* Chronic Gastritis

- In Malt lymphoma the prevalence of *H. pylori* infection is 90% Vs 96% in our series.
**Helicobacter pylori**

- gram-negative spiral microaerophilic bacterium
- *campylobacterales* order, *Helicobacteracea* family
- capable to colonize the hostile environment of the human stomach
- Secreting urease to neutralize the local acid pH.
- Since its successful isolation in 1983 by Warren and Marshall, *H. pylori* has been linked to various pathologies and a strong association with gastric carcinoma and GL’M’ (carcinogen class I : OMS 1994)
- Over 50% of the world’s population carries this infection, in Algeria more than 90% of general population are *Hp* infected (Megraud, 1989)
NOBEL Prize of Medicine 2005
Warren & Marshall
Infection rates vary among the developed and developing countries of the world

- decline in most of the western countries mainly due to the success of combination therapies and improved personal hygiene and community sanitation to prevent re-infection

- However, the situation is not improving in many of the developing countries like in Algeria
**HELICOBACTER Pylori**

- *Hp* infection -> acquired during childhood
- Transmission occurs predominantly within families
- *Hp* causes chronic active gastritis, only a small minority (1 – 2%) develop a malignant disease (gastric carcinoma and GL’M’)
- Distinct genotypes have been found to be associated with particular geographic regions
- The *cag* pathogenicity island (*cag* PAI) and the *cagA* gene are principle virulence factors within the *Hp* strains.
Clinical features

- Non specific symptoms
  - Abdominal pain: most common presenting symptom
  - Dyspepsia, nausea, vomiting...
  - Palpable epigastric mass, Weight Loss...

- At endoscopy:
  - Enlarged gastric folds, gastritis
  - Superficial erosions
  - Suspect antral ulceration (> 80% of cases)
G’M’L : Macroscopy appearance
Gastric Lymphoma

Histological Classification (OMS 2008)

- MALT L (G 'M' L)
- Diffuse large B cell L
  - Diffuse large B cell L + MALT L component
- Others: rares / Mantle cell L (cycline D1), FL (CD10, Bcl2), CLL (CD5), Burkitt L, T L (HTLV1), HDK ...
Histological features
G’M’L (1)

- Closely simulate those of a Peyer’s plaque

- **Stereotypy**
  - Neoplastic cells infiltrate around reactive B-cell follicles
  - Marginal zone cell distribution and spreading outwards → diffuse to lamina propria

- **Reactive non neoplastic follicles**
  → Important component of MALT L.
  → Often colonized
Histological features: G'M'L (2)

- Exhibit a variety of cytological appearances with
  - Lymphocytic cells: small to medium sized, small irregular nuclei characteristic of centrocyte-like cells (CLC)
  - monocytoid B-cells with abundant pale cytoplasm and well defined cell borders
  - Scattered large transformed Centroblast or immunoblast-like cells usually dispersed

- Variable numbers of plasma reactive cells are frequently present beneath the surface epithelium, a few of them may be proliferative monoclonal cells
Histological features: G’M’L (3)

- **Lymphoepithelial lesions (LEL):** Characteristic feature
  - Invasion of individual crypts by aggregates (≥ 3) of Centrocyt Like Cell (CLC)
  - Degenerative changes + disintegration of the crypt epithelium (oncocyte-like)
Histological features: G’M’L (4)

- Foci of DLBCL may be seen suggesting that there has been transformation from one to the other (Isaacson:1 -10% of blastic cells in cluster of 20 cells or diffuse infiltrate of blastic cells = high grade component)

Progression to DLBCL

- Islands or clusters of 20 blastic cells
- Diffuse infiltrate of large cells
In our series, 2/3 (157/244: 65%) of gastric lymphoma are of MALT type \(Hp\) associated. The others (87/244: 1/3) are DLBCL with G’M’L component.

- 96% of GL are associated to \(Hp\) gastritis
Two components

1. Malignant
   - Lymphocyt cells centrocytic - like
   - Monocytoid cells
   - Plasmacytoid cells
   - Expanded confluent marginal zones
   - Scattered large transformed centroblast or immunoblast-like cells
   - Lymphoepithelial lesions

2. Reactive
   - Reactive germinal centers may be colonized by marginal zone cells
G ’M’ L
Immunophenotype
No specific phenotype

- They are typically CD20+
  - and B marker like CD19, CD79a...
  - CD43+ sometimes,
  - BCL-2+
  - CD5 and CD10 negative
  - express surface and cytoplasm immunoglobulin (IgM, few IgA or IgG)
  - Light chain restriction sometimes
G‘M’L : Immunophenotype

CD 20
- CD21, CD23 or CD35 can be used to highlight colonized follicles
- EMA can be used to highlight lymphoepithelial lesions
- Bcl-10 over expression confers an increasing capacity of an autonomous development of GL, so no responding to tritherapy
Differential diagnosis
**Difficulties of diagnosis specific to the G ‘M’ L**

- Diagnosis relatively easy on gastrectomy specimen, can be difficult on biopsies
  - especially if they are very few, of small size and crushed → research of histological criteria of GL’M’
  - LEL ≠ lymphoepithelial images (chronic gastritis with severe intensity) → histological scoring of lymphoid infiltrations in the stomach according to Wotherspoon and colleagues (Gut, 2006) may be helpful
### Histological scoring of lymphoid infiltrations in the stomach according to Wotherspoon (Gut, 2006)

<table>
<thead>
<tr>
<th>Score</th>
<th>Diagnosis</th>
<th>Histological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>Scattered plasma cells in lamina propria (LP). No lymphoid follicles</td>
</tr>
<tr>
<td>1</td>
<td>Chronic active gastritis</td>
<td>Small clusters of lymphocytes in LP. No lymphoid follicles. No LEL</td>
</tr>
<tr>
<td>2</td>
<td>Chronic active gastritis With florid lymphoid follicle formation</td>
<td>Prominent lymphoid follicle with surrounding mantle zone and plasma cells. No LEL (lymphoepithelial lesions)</td>
</tr>
<tr>
<td>3</td>
<td>Suspicious lymphoid infiltrate, probably reactive</td>
<td>Lymphoid follicles surrounded by small lymphocytes that infiltrate diffusely in LP +/- into epithelium</td>
</tr>
<tr>
<td>4</td>
<td>Suspicious lymphoid infiltrate, probably lymphoma</td>
<td>Lymphoid follicles surrounded by marginal zone cells that infiltrate diffusely in LP and into epithelium in small groups</td>
</tr>
<tr>
<td>5</td>
<td>MALT lymphoma</td>
<td>Dense infiltrate of marginal zone cells in LP with proeminent LEL</td>
</tr>
</tbody>
</table>
G‘M’L

Differential diagnosis on Bx

- Malt type L Vs florid acquired Malt in CG
  - sometimes difficult → multiples specimen, better directed
  → morphological arguments / IHC

Floride acquired MALT

G ‘M’ L
IHC: monoclonality

Kappa

Lambda
Difficulties of diagnosis specific to the G‘M’L

- G ‘M’ L Vs another type of small B-cell lymphoma
  - Follicular lymphoma : CD 10, Bcl2, Bcl6
  - Lymphocytic lymphoma : clinique, CD5, CD43, CD23
  - Mantle cells lymphoma (lymphomatose polyposis) →
    cells with same cleaved feature (centrocyte - like) :
      - Activated cells + respected **germinatives centers**
        + LEL exceptional
      - Gastric localization is rare, characteristic
        endoscopic aspect, fast dissemination and fatal
        evolution may help for diagnosis
    - IHC (cycline D1)
Difficulties of diagnosis

- DLBCL with MALT type component Vs MALT lymphoma (on superficial specimen): 1 to 10% of blastic cells in cluster of 20 cells are in favor of high grade component (Isaacson)

- DLBCL with cluster of 20 blastic cells Vs colonized residual follicle center: IHC using CD21 or CD23 may be help to differential diagnosis between cluster of blastic cells and colonized follicle

- On undifferentiated zones: Alcian Blue highlighting mucins, a poor differentiated carcinoma with mucipares cells can be diagnosed; IHC: EMA, CK
Differential diagnosis on Bx

- **DLBCL Vs germinatif résiduel center**
  - Islands or clusters of 20 blastic cells
  - Dc # : colonized *germinatif résiduel center* (cfd CD23+)

Images:
- **CD23 germinal center**
- **CD23 Malt L**
- Organoid net work of Fol. dentr.
- Disorganized net-work
Differential diagnosis on Bx

- **DLBCL Vs indifferenciated carcinoma**
  - Dc # : morphologic features / nuclei
  - histochemistry stains / Giemsa, AB
  - IHC / EMA, CD 20
Histological evaluation after early G’M’L *Hp* eradication

Wundisch Histological grading (J. Clin. Oncol, 2005)
**H pylori** and early Gastric MALT Lymphomas

- **Triple therapy** for one week (OAM / OAC)
  - Omeprazole 20mg 2x/d
  - Amoxycillin 1000mg
  - Metronidazole 500mg or Clarythromycin 500mg
  Few cases required 3 to 4 cures for *Hp* eradication (45 d interval)

- **Follow up examination** including endoscopy and histology
  3 m intervals / two y, every 6 m then after

- **Histological grading for evaluation**
Evaluation of histological response of early G’M’L after *Hp* eradication: Wundisch Histological grading

(J. Clin. Oncol, 2005)

- Best method of post treatment follow up
  - Serial endoscopy with histological assessment of multiples biopsies (and ultrasound endoscopy)

- Grading describes 5 levels of response using 3 factors:
  - Lymphoid infiltrate
  - LEL
  - And stromal changes

- Results may be complete remission CR, histological residual disease hRD, partial remission PR and no change NO or progression of the disease PD
Evaluation of histological response of early G’M’L, after *Hp* eradication


In our serie 61 of 157 patients (39%) with early MALT lymphoma, had *Hp* eradication:

- 57% CR (Vs 60 à 90 % : Fischbach study, 2004) that needs: 2 successives negatives biopsies with multiple specimens and a mapping to confirm the CR
- 21% hRD (vs 18%, Fischbach) : No therapeutic nor prognostic signification, so a watch and wait strategy must applied
- PR and NC Vs PD : 20% (vs 16%) show after sequential biopsies a blastic component; low and high grade component may be synchronous in GL so that needs a gastric mapping which minimizes sampling errors
Histological eradication therapy response depends on:

- Histological lymphoma grade
- **Stage** (nodes infiltration and depth infiltration assessed by endoscopic ultrasonography)
- Associated **genetics abnormalities**
  
  / t(11,18); t(1,14)

  IHC study using Bcl-10: Nuclear +ve
Eradication therapy: simple, efficient

regression --> 56 à 100%

Wotherspoon, 1993: 5/6 cases
Bayerdorffler; 1997
Isaacson, 1999: 6/6 cases
Fischbach, 2002-2004: 56/90 cases
Wundisch, 2005: 96/120 cases
Amir et al., 2007: 35/61 cases
Shiho, 2008: 66/74 cases

- **CR**: 2 series successive Bx (-) / multiples specimens generally obtained between 6 -18 months after Therapy

- **No response** ---+ Foci of large cells!
  - t (11;18) / t(1;14)

- **hRD monoclonal persistence**: no signification
Molecular pathology
A number of genetic and epigenetic abnormality have been described (Isaacson, 2005):

- $t(11,18)(q21;q21)$, $t(1;14)(p22;q32)$, $t(14;18)(q32;q21)$
  - 3 chromosomal translocations are specifically associated with Malt Lymphoma
  - Role in diagnosis, prognosis

- Trisomies 3 (60%), 12 and 18 less frequent

- $p53$ LOH/mutation, $p15$, $p16$ promoter methylation...

- $PAX5/IGH$
**T(11;18) MLT and API2 genes**

- **t (11;18) (q21; q21)** in 30-40% MALT L
  - caused reciprocal fusion of the API2 and MALT1 genes
  - not been detected in MALT with DLBCL
  - This kind of lymphoma gain autonomous growth ability and resistant to *Hp* eradication
Other mutations

- t(14;18) (genes *IGH* and *MLT*)
  cytogenetically similar but molecularly distinct from follicular lymphoma

- t(1;14)(p22;q32) and t(1;2)(p22;p12) < 5%:
  exclusive *Hp* independent - GL ‘M’ and those may undergo high grade transformation; this translocation juxtaposes BCL-10 to an immunoglobulin gene locus thus deregulating its expression
Bcl-10

- t (1;14) and t (1;2) involve the bcl-10 gene
  = Advance stage of lymphoma
- t(11;18) does not involve the bcl-10 gene

- Nuclear bcl-10 immunohistochemistry detects both t(11;18) and t(1;14)
Pathogenesis of gastric MALT lymphoma
Pathogenesis of G’M’L

- Normal gastric mucosa is devoid of lymphoid tissue
- Multistage process starting with *Hp* infection
  - stimulating *Hp*-specific T-cell clones
  - B cell follicles
  - promotes malignant transformation of reactive B-cells due to acquisition of genetics abnormalities
  - induces and sustains an active proliferating B-cell population that may develop genetic abnormalities
  - attracting and activating neutrophils, which release oxygen reactive species = genotoxic and causes genetic abnormalities
Chronic *Hp* infection

Acquired MALT

*Hp* specific T cells

B cells proliferation

65%

Trisomies 3, 12, 18

Early MALT Lymphoma

65%

Advanced MALT Lymphoma

Trisomies 3, 12, 18

T(1;14) (p:22;p:32)

MALT Lymphoma

5%

Advanced MALT Lymphoma

5%

T(1;14) (p:22;p:32)

MALT Lymphoma

30%

t (11;18) (q:21; q21)

MALT Lymphoma

Direct Ag stimulation

*Hp* dependent

*Hp* independent

*Hp* dependent

*Hp* independent
■ Helicobacter pylori play a crucial role in the development and progression of gastric lymphoma.

■ GL is a relatively prevalent gastric malignant tumor; GL’M’ is an indolent disease but may become locally aggressive, spread, or undergo high grade transformation.

■ True prolonged remissions are possible right by Hp eradication treatment.
Eradication therapy is efficient and simple; it permitted the regression of more than a half of early gastric MALT lymphomas in our Hp positive patients. Careful endoscopic evaluation with multiple biopsy and endoscopic ultrasonography would help in staging and monitoring patients.
Histological diagnosis depends on
- clinical data information,
- MALT sites exploration with multiple directed and performed biopsy specimens (gastric mapping with more than 20 specimens in order to identify a high grade component)
- best histological techniques with good HE and CD20 (IHC)

Immunohistochemistry, molecular biology would allow a better comprehension of these GL for better treating and why not preventing them by vaccination.
XXVII International Congress of the IAP
Athens, Greece 2008
THANK YOU
REFERENCES


Cologlione SB. Primary B cell gastric lymphoma : a clinicopathological study of 145 cases. Gastroenterol 1997 ; 101 : 1159-1170.0


Fischbach W. Prevalence of H.Pylori gastric lymphoma of the MALT There is difference between low grade and high grade lymphoma ;Gut 1995, 37(suppl 2), A 75.

Fischbach W et al; GUT 2004; 53: 34–37


Koch P. Primary gastric lymphoma. world congress on gastrointestinal cancer. Barcelona, 15-18 June 2005


Strains expressing the CagA proteine. Gastroenterology 1997 ; 112 : 1482- 1486.


